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Adhesion

Its Role in Inflammatory Disease

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and
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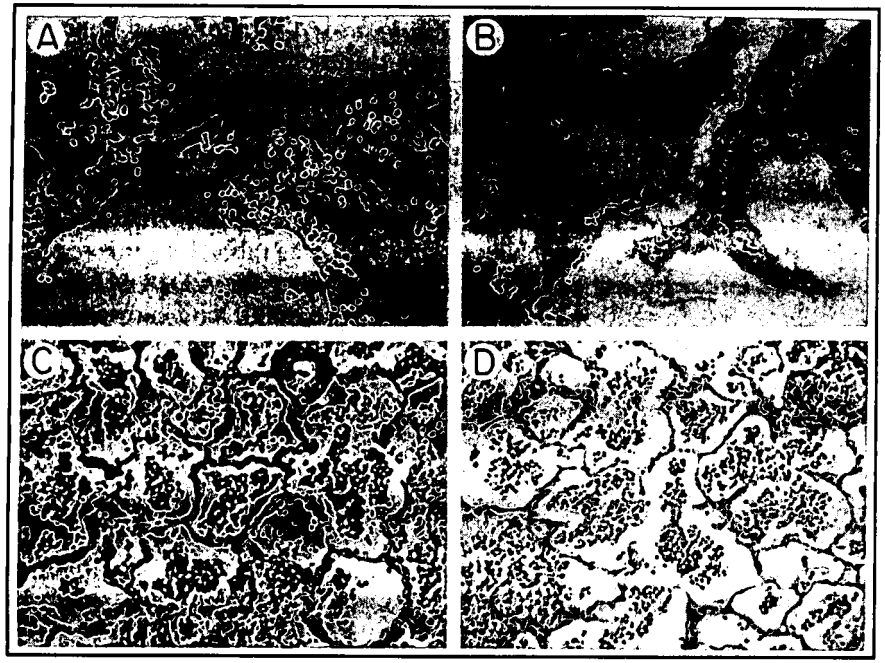

Figure 6-2. CD18-dependent and -independent mechanisms of neutrophil emigration. Neutrophil migration in response to *S pneumoniae*-induced inflammation was assessed in a control animal or an animal pretreated with the CD18 MAb 60.3 (2 mg/kg). *A*, *S pneumoniae*-containing sponge in control animal showing infiltration of sponge by neutrophils. *B*, *S pneumoniae*-containing sponge in animal pretreated with MAb 60.3, showing complete absence of neutrophils. *C*, lung of control animal after instillation of *S pneumoniae*, showing accumulation of neutrophils in alveoli. *D*, lung of MAb 60.3-treated animal (same animal as in *B*) following instillation of *S pneumoniae*, showing accumulation of neutrophils in alveoli. Adapted from Doerschuk, C.M., Winn, R.K., Coxson, H.O., and Harlan, J.M. (1990) *J. Immunol.* 144, 2327–2333 with permission.

could potentially induce expression of new adhesive ligands on the endothelium or activate different adhesion receptors on the leukocyte. This possibility is supported by the studies of Mileski et al.[64] who showed that the CD18-independent "phenotype" could be induced in normal peritoneum by the recruitment of macrophages. In these studies, neutrophil emigration into rabbit peritoneum was elicited by instillation of *E coli* or *S pneumoniae* organisms with or without pretreatment with the CD18 MAb 60.3. Peritoneal lavage was performed four hours after instillation of organisms and the number of neutrophils was determined. In the normal peritoneum, the CD18 MAb produced nearly 90% inhibition of neutrophil emigration. However, if the peritoneum was first "primed" by instillation of protease peptone 72

hours prior in order to elicit a macrophage-rich exudate, then the CD18 MAb only minimally inhibited *S pneumoniae*-induced emigration (36%), although it still inhibited *E coli* emigration by nearly 90%. If the "primed" peritoneum was washed to remove macrophages prior to instillation of *S pneumoniae* organisms, neutrophil emigration was again inhibited by nearly 90% by the CD18 MAb. Finally, instillation of macrophages obtained from protease peptone-treated animals into normal animals significantly reduced the inhibition produced by the CD18 MAb (48%). Overall, these results demonstrate that the CD18-independent mechanism of emigration that is observed in the pulmonary microcirculation in response to *S pneumoniae* organisms can be induced in the systemic microcirculation by maneuvers that augment the number of macrophages in the peritoneal cavity. The macrophage-generated product(s) elicited by *S pneumoniae* organisms and the adhesion molecules involved in this CD18-independent pathway remain to be identified.

ICAM-1

Intercellular adhesion molecule-1 (ICAM-1, CD54)[77,78] and ICAM-2[79] are ligands for CD11a/CD18. ICAM-1 is expressed at low levels on endothelium *in vivo*, and is up-regulated in response to inflammatory stimuli. ICAM-2 is constitutively expressed on endothelium. CD11a/CD18 recognizes both ICAM-1 and ICAM-2. Studies by Smith et al.[80] and by Diamond et al.[81] indicate that ICAM-1 is also a ligand for CD11b/CD18. Monoclonal antibodies to ICAM-1 have been demonstrated to inhibit lymphocyte and neutrophil emigration to tissues in several models of inflammation and immune reaction[68,70,82,83] (Table 6-1).

L-Selectin

The L(leukocyte)-selectin (LECAM-1, LAM-1) was first described in the mouse as the MEL-14 antigen, the "homing" receptor for lymphocyte binding to high endothelial venules of peripheral lymph nodes.[1] Lewinsohn et al.[84] showed that the MEL-14 antigen was also present on granulocytes and lymphocytes and that the MEL-14 MAb inhibited the binding of neutrophils and monocytes to inflamed high endothelial venules in tissue sections and at sites of acute inflammation in the skin. Subsequently, Jutila et al.[85] showed that MEL-14 also inhibited neutrophil accumulation in inflamed peritoneum. These observations using the MEL-14 MAb were confirmed by Watson et al.[86] using a soluble immunoglobulin chimera containing the murine homing receptor extracellular domain (LEC-IgG). Administration of LEC-IgG significantly decreased the number of neutrophils that migrated to the peritoneum in response to the inflammatory irritant thioglycolate. Watson